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DERMAL PENETRATION AND DISTRIBUTION OF 14C-LABELED  
1-(3-CYCLOHEXEN-1-YL-C<sub>6</sub>H<sub>5</sub>)<sub>2</sub> (U) ARMY ENVIRONMENTAL HYGIENE  
AGENCY ABERDEEN PROVING GROUND MD H L SNODGRASS MAR 84

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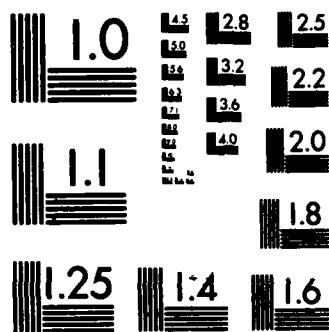
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UNITED STATES ARMY  
ENVIRONMENTAL HYGIENE  
AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

PHASE 1  
DERMAL PENETRATION AND DISTRIBUTION OF  $^{14}\text{C}$ -LABELED  
1-(3-CYCLOHEXEN-1-YL-CARBONYL) PIPERIDINE. AIG-35765  
STUDY NO. 75-51-0234-84  
OCTOBER 1983 - MARCH 1984

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The candidate insect repellent 1-(3-cyclohexen-1-yl-carbonyl) piperidine, AI3-35765, was assessed for skin absorption potential in rats and dogs by monitoring radiocarbon in excreta for 7 days following a single application. In both species, absorption occurred primarily in the first 24 hours and measured 32 percent of the applied dose in rats and 21 percent in dogs through 7 days. No marked bioaccumulation in animal tissue specimens was noted at necropsy by this route. Absorption in man should be less than 12 percent of a topical dose. 71		



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SUBJECT: Phase 1, Dermal Penetration and Distribution of <sup>14</sup>C-Labeled 1-(3-Cyclohexen-1-yl-carbonyl) piperidine, AI3-35765, Study No. 75-51-0234-84, October 1983 - March 1984

Executive Secretary  
Armed Forces Pest Management Board  
Forest Glenn Section, WRAMC  
Washington, DC 20307

#### EXECUTIVE SUMMARY

The purpose, essential findings, and conclusions of the inclosed report follow:

a. Purpose. 1-(3-Cyclohexen-1-yl-carbonyl) piperidine, AI3-35765, is a promising insect repellent. As such, its skin absorption potential and bodily distribution was assessed in rats and dogs using the radiolabeled (<sup>14</sup>C) chemical.

b. Essential Findings. Absorption of topical AI3-35765 measured 32 percent of the applied dose in rats and 21 percent in dogs through 7 days. Urinary excretion accounted for nearly all of the recovered/absorbed chemical in dogs. In rats, additional excreted radiocarbon was recovered in feces. After a single intravenous injection to both species, nearly all of the recovered chemical appeared in excreta within 24 hours. At necropsy, tissues from animals treated topically showed no marked accumulation of radioactivity.

c. Conclusions. The dermal absorption of AI3-35765 in man would be expected to be lower than that demonstrated in animals, probably less than 12 percent of the applied dose. Metabolic elimination of the absorbed chemical is rapid and occurs primarily through urinary excretion. No marked internal retention of labeled AI3-35765 metabolites was observed in animals following dermal application.

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USDA, ARS (Dr. Terrence McGovern)  
Cdr, USAMRDC [SGRD-DPM/LTC(P) Reinert]

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PHASE 1  
DERMAL PENETRATION AND DISTRIBUTION OF  $^{14}\text{C}$ -LABELED  
1-(3-CYCLOHEXEN-1-YL-CARBONYL) PIPERIDINE, AI3-35765  
STUDY NO. 75-51-0234-84  
OCTOBER 1983 - MARCH 1984

1. AUTHORITY.

a. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the Department of Agriculture, Agricultural Research, Science and Education Administrations; titled Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

b. Letter, AFPMB, Armed Forces Pest Control Board, 29 November 1979, subject: Toxicological Testing of Candidate Repellent Compounds, with inclosure.

2. REFERENCES.

a. Final Rule, Pesticide Programs; Good Laboratory Practice Standards: 48 Federal Register (FR) 53963-53969, 29 November 1983.

b. Toxicology Division Standing Operating Procedure, Radicisotope Studies, US Army Environmental Hygiene Agency (USAEHA), February 1983.

3. PURPOSE. The purpose of this study was to quantitate the rate of penetration of  $^{14}\text{C}$ -labeled AI3-35765 through the intact skin of rats and dogs following a single topical application. The resultant absorption and bodily distribution of the chemical was assessed by monitoring radioactivity in excreta for 7 days and selected tissues at necropsy. The kinetics of labeled AI3-35765 following intravenous administration were also determined.

4. SPONSOR. Armed Forces Pest Management Board (AFPMB), Washington, DC.

5. GENERAL.

- a. See Appendix A for Results.
- b. See Appendix B for the Bibliography.
- c. See Appendix C for Analytical Quality Assurance information.

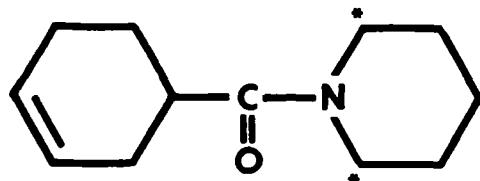
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6. BACKGROUND. AI3-35765 is a candidate insect repellent proposed for use by military personnel as a topically applied solution on human skin or clothing impregnant. As such, its dermal absorption and metabolism is of toxicological importance. The albino rat was used because of its acceptance by Federal regulatory agencies in general metabolism studies (reference 2a). The Beagle dog was used because, compared to the other available animal models, it more closely resembles man's absorption kinetics. The methodology for assessing absorption potential of radiolabeled compounds in animals has been previously described (reference 2b).

7. MATERIALS.

a. Radiolabeled 1-(3-cyclohexen-yl-carbonyl) piperidine (piperidine-2,6  $^{14}\text{C}$ ), AI3-35765, was synthesized by and purchased from New England Nuclear, Boston, Massachusetts. It was identified as lot no. 1181-251 and contained a reported radiochemical purity of 98 percent as determined by thin layer chromatography and radiochromatogram. Specific activity was 22 millicuries per millimole.

b. The chemical structure of AI3-35765 is as follows:



c. Ninety-five percent ethyl alcohol was the diluent used in all AI3-35765 solutions for animal administration.

8. ANIMALS.

a. Twelve male rats, weighing between 200 and 250 g, were randomly selected from the USAEHA breeding colony. Animals were offspring of Charles River Sprague-Dawley COBS rats, purchased originally from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Animals were housed in individual Nalgene metabolism cages and received food (Formulab Chow #5008, Ralston Purina Company, St. Louis, Missouri) and water ad libitum. Six rats received the test compound dermally and six intravenously.

b. Six purebred Beagle dogs, 1-year old, were selected from USAEHA kennel stock. Animals were originally purchased from Laboratory Research Enterprises, Kalamazoo, Michigan. Dogs were housed in individual Wahmann metabolism cages and received food (Respond 2000, ProPet, Inc., Syracuse, New York) and water ad libitum. Three dogs were treated dermally and three intravenously.

9. METHODS.

a. Six rats each received a single intravenous injection of  $^{14}\text{C}$ -labeled AI3-35765 to assure that systemic elimination of the chemical was measurable in excreted urine. Injection was made into the femoral vein while the animal was under light ether anesthesia. Each rat received a radioactive dose of 4.54 microcuries ( $\mu\text{Ci}$ ) and a chemical mass of 40 micrograms ( $\mu\text{g}$ ) contained in a 0.01 mL injection volume.

b. Six rats each received the chemical topically as a single dose. The mid-lumbar area of the back was clipped free of hair and the application area demarcated with petrolatum to contain the chemical within the predetermined 1  $\text{cm}^2$  area. The applied dose was 40  $\mu\text{g}$  (4.54  $\mu\text{Ci}$  radioactivity) for an application rate of 40  $\mu\text{g}/\text{cm}^2$ . The application area was then covered with a nonocclusive patch which protected the area without contacting the radiochemical. The patch was changed at 24 hours.

c. Dogs also received labeled AI3-35765 as a single intravenous or topical dose. Three dogs were treated intravenously with 400  $\mu\text{g}$  of the chemical. Injection (0.1 mL) was made into the cephalic vein using a small amount of saline as a carrier. The remaining three dogs each received a 400  $\mu\text{g}$  dose topically to a 10  $\text{cm}^2$  area (40  $\mu\text{g}/\text{cm}^2$ ). The area was covered with a nonocclusive patch and changed at 24 hours. The radioactive dose delivered to each dog was 45.4  $\mu\text{Ci}$ .

d. Blood specimens were collected at timed intervals from dogs injected with  $^{14}\text{C}$  AI3-35765 to assess disappearance of radiocarbon from circulating blood. A semilog plot of radioactivity in blood versus time was constructed using the "stripping" technique. The half-life ( $t_{1/2}$ ) was determined for the rapid distribution (alpha) phase and the slower elimination (beta) phase.

e. Excreta was collected and measured from all animals at 24-hour intervals through the 7-day test period. Aliquots (0.2 mL) of urine were combined with 15 mL of PCS<sup>®</sup>II scintillation cocktail and radioactivity measured using a Beckman Model LS 9000 Liquid Scintillation Counter. Internal standardization techniques and automatic quench correction procedures were employed. Feces were collected daily, weighed, and combined with 2 volumes of methanol. After mixing for 24 hours, aliquots (0.2 mL) of the supernate were combined with PCS II and counted.

f. At the end of the study period, all animals were euthanized and representative tissue and fluid specimens collected and measured for radiocarbon content. Specimens included liver, lung, kidney, spleen, heart, brain and adrenal glands. Also collected were urinary bladder, muscle, bone, skin, fat, thyroid gland, testes, bone marrow, blood and bile. Radioactivity was assessed following oxidation of each 0.25 - 0.45 g specimen to  $^{14}\text{CO}_2$  using a Packard Biological Materials Oxidizer.

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● PCS II is a registered trademark of Amersham Corp., Arlington Heights, Illinois. Use of trademarked names does not imply endorsement by the US Army, but is intended only to assist in the identification of a specific product.

g. Unabsorbed AI3-35765 from topically treated animals was quantitated by extracting the nonocclusive patches and the excised skin from the application site in methanol. Extract fractions (0.2 mL) were combined with PCS II and counted.

h. Excretion rates of radiocarbon were calculated as the percent recovery each day of the injected or applied dose appearing in urine or feces. Calculations for tissue specimens collected at necropsy were based on counts (cpm) per specimen and reported as dpm/g of wet tissue following correction for counting efficiency.

## 10. RESULTS.

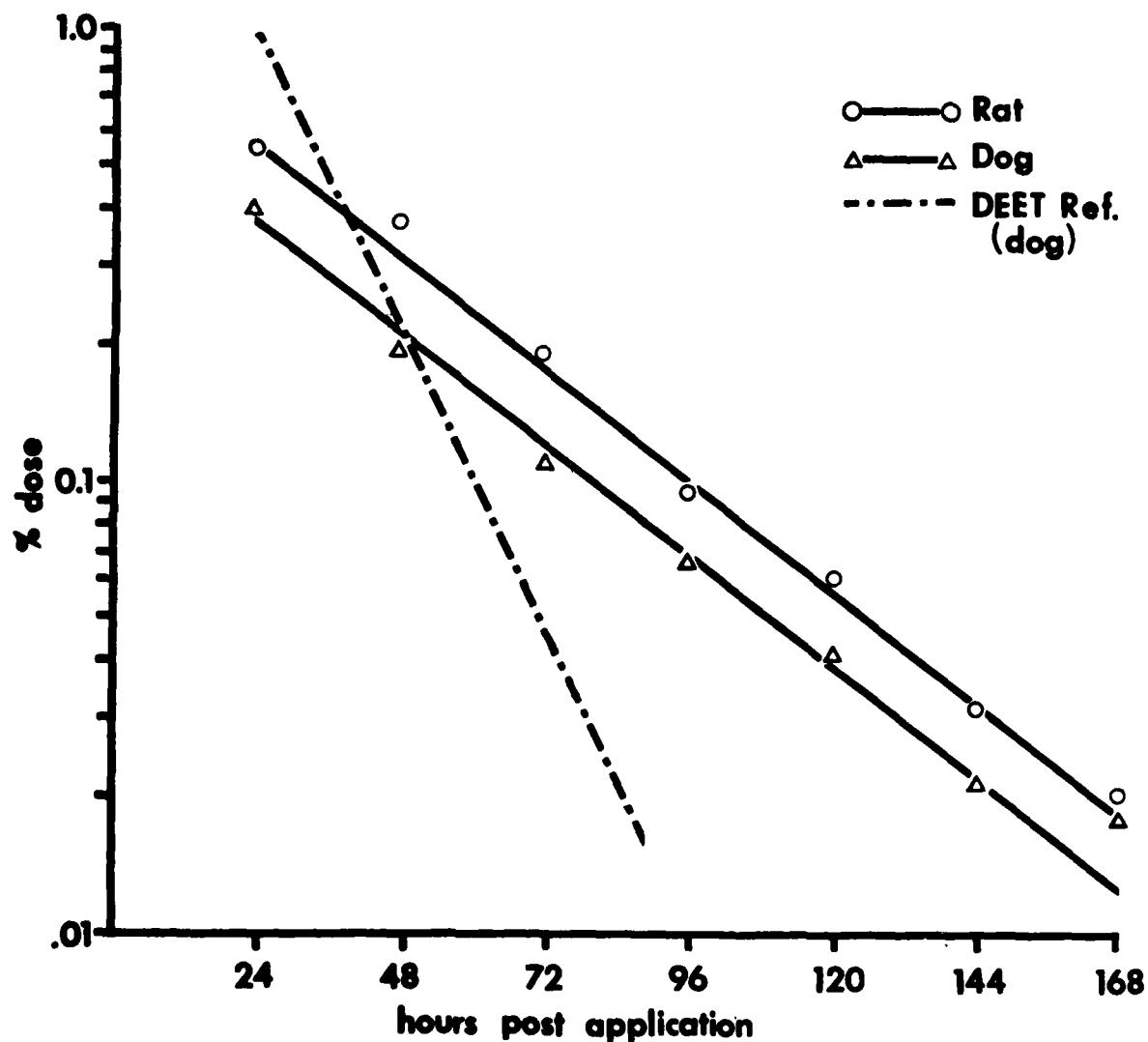
a. Intravenous Injection. Urinary excretion was the predominant elimination pathway in both rats and dogs following a single intravenous injection of AI3-35765. Nearly all of the radiocarbon excreted in urine appeared within the first 24 hours, about 50 percent of the injected dose in both species (Table A-1, Appendix A). One percent or less was eliminated in urine between days 3 and 7. Radioactivity appearing in the feces, enteric elimination, measured 22 percent in rats and 8 percent in dogs through 7 days (Table A-1, Appendix A). The elimination pattern was similar to that noted for urine, though in dogs, radiocarbon levels in feces were higher at 48 hours than at 24. Tissue specimens collected 7 days after injection of AI3-35765 showed measurable radioactivity in most of the tissues monitored in rats and dogs (Table A-2, Appendix A). The spleen and liver registered the highest concentration of radiocarbon followed generally by the kidney, heart, lungs and adrenal glands. Only brain specimens from both species were void of detectable radioactivity. The total body-burden of radiocarbon at 7 days measured about 2 percent of the injected dose in both species. The half-life ( $t_{1/2}$ ) disappearance of radioactivity from circulating dog blood following intravenous injection was 95 minutes for the alpha phase. The  $t_{1/2}$  of the slower beta phase elimination was an estimated 13 hours.

b. Topical Application. Recovery of absorbed  $^{14}\text{C}$ -labeled AI3-35765 following topical application to rats and dogs is shown in Table A-3, Appendix A. In rats, 23 percent of the applied chemical was excreted in urine through 7 days. An additional 9 percent appeared in feces. The greatest quantitative absorption, as measured by radiocarbon in urine, occurred in the first 24 hours. Lesser, though significant amounts were absorbed through 4 days. In dogs, absorption of AI3-35765 totaled 21 percent of the applied dose through 7 days as measured in excreta. Only 2 percent was contributed by feces. The absorption/elimination rate was nearly identical in both rats and dogs through the entire study period as seen in the Figure. Deposition of radiolabeled AI3-35765 in animal tissues 7 days after a topical application is shown in Table A-2, Appendix A. No marked accumulation of radiolabeled moieties was apparent in any separate tissue. In dogs, terminal bile specimens contained the highest measurable radiocarbon. Unabsorbed AI3-35765 was recovered from the application site after 7 days and from the nonocclusive patches at days 1 and 7 (Table A-4, Appendix A). Twenty-three percent of the applied dose in rats and 51 percent in dogs was recovered unabsorbed.

FIGURE

**Mean Excretion (Absorption) Rate of Topically Applied A13-35765  
to Animals**

PERCENT DOSE PER HOUR



11. DISCUSSION.

a. A pharmacokinetic model attempts to describe the bioavailability of a xenobiotic in a test species. Bioavailability represents that portion of administered dose gaining access to the pharmacologically reactive sites of the host system. A single intravenous bolus of a compound maximizes this potential though is generally not representative of intended or accidental exposure. It is, however, of value in assessing the body's efficiency for metabolic degradation and removal of exogenous chemicals. Since the clearance of injected AI3-35765 in animals was rapid, it follows that radiocarbon appearing in excreta after a topical application, being quantitatively lower, should accurately reflect absorption potential in the species tested.

b. Excretion data from both animal species following topical application of labeled AI3-35765 suggested a significant rate limiting effect of the dermal barrier. No more than about 10 percent absorption occurred in either species for any 24-hour period. In comparison, DEET\*, a commercially available insect repellent, was readily absorbed by dogs in a similar test; 22 percent of the dose appeared in urine within 24 hours of topical application and totaled 30 percent through 7 days.<sup>2</sup> As noted in the Figure, the daily decline in AI3-35765 absorption rate was nearly identical between rats and dogs and follows first-order kinetics throughout the 7-day test. It may be assumed that in man, similar kinetics would be followed although quantitative absorption should be lower than that demonstrated in animals.<sup>3,4</sup> It is important to note that the topical dose used here in dogs (400 µg/cm<sup>2</sup>) represents what may be expected from the application of a thin film of a 25 percent repellent formulation.<sup>5</sup>

c. Evaporation of topical AI3-35765 from the skin surface in dogs was significant (43 percent) through 7 days but was impossible to totally quantitate. Radiocarbon recovered from the nonocclusive patches gives some indices of volatilized chemical trapped in the patch. The "breathable" patches, by design, allow the escape of evaporating material thereby sacrificing some accountable radioactivity. In rats, difficulties in maintaining the patches intact beyond the first 24 hours were encountered, hence, the reduced recoveries.

d. No significant loss of radiolabeled AI3-35765 was attributed to expired <sup>14</sup>CO<sub>2</sub> in rats following an intravenous injection. Preliminary tests in this laboratory have demonstrated that less than 2 percent of the injected radiocarbon appeared in expired air through 8 hours. Radioactivity peaked between 40 and 60 minutes after injection then gradually decreased through the balance of the test period.

e. Tissue distribution of radiocarbon 7 days after topical application of AI3-35765 to rats and dogs showed no trends for selective deposition in any extrahepatic tissue or organ system. This may be attributed to the rate limiting effecting of the dermal barrier in contrast to an intravenous

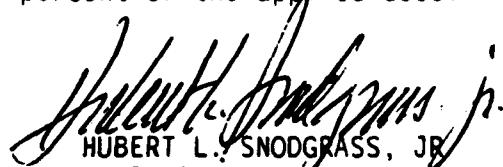
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\* N,N-diethyl-m-toluamide

bolus. Tissues from animals treated intravenously showed consistent retention of radiocarbon 7 days after treatment. Highly perfused tissue, i.e., spleen, liver, heart, and lung, was most affected. This suggests a first-pass binding effect, perhaps of the intact labeled molecule. In tissues having lesser blood flow, radiocarbon levels were seldom higher than comparable term blood levels. This would indicate that the labeled metabolites are not strongly lipophilic.

f. The metabolic degradation of AI3-35765 in animals has not yet been characterized. Certain general assumptions can, however, be made. Piperidine is a strong base ( $pK_a$ , 2.8), therefore, much of it might be expected to be excreted unchanged as has been observed in rabbits and fowl.<sup>6</sup> There is no evidence that it is methylated *in vivo* or undergoes dehydrogenation to pyridine derivatives.<sup>6</sup> Piperidine is a normal constituent of human and animal urine and man excretes 3-20 mg/day.<sup>6</sup> The remaining AI3-35765 moiety, cyclohexene, may be converted to cyclohexene oxide by the direct addition of oxygen to the double bond. Alkenes characteristically undergo reaction with perbenzoic acid or other oxygen contributors to form epoxides.<sup>7</sup> The toxicity implications depend greatly on the reactive nature of the epoxide intermediate<sup>8</sup> and by the dose level of the test chemical.<sup>9</sup>

12. CONCLUSIONS. Within the intended use of AI3-35765 as a topical insect repellent, absorption/bioavailability in man would be expected to be lower than that observed in dogs, probably less than 12 percent of the applied dose through 7 days of contact. Urinary excretion is the primary elimination pathway of absorbed chemical. Metabolic elimination of labeled moieties is rapid, occurring within 24 hours of fractional absorption. No potential for bioaccumulation in animal tissues has been noted following dermal application at 400  $\mu\text{g}/\text{cm}^2$ . Evaporation of AI3-35765 from the skin surface probably exceeds 50 percent of the applied dose.



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Phase 1, Study No. 75-51-0234-84, Oct 83 - Mar 84

APPENDIX A

TABLES

TABLE A-1. EXCRETION OF  $^{14}\text{C}$ -LABELED AI3-35765 FOLLOWING INTRAVENOUS INJECTION TO RATS AND DOGS

PERCENT OF INJECTED DOSE		
RATS (n = 6)		
Day	Urinary Excretion	Fecal Excretion
1	50.75 $\pm$ 4.08	18.34 $\pm$ 0.89
2	2.61 $\pm$ 0.75	2.32 $\pm$ 0.47
3	0.67 $\pm$ 0.17	0.53 $\pm$ 0.11
4	0.27 $\pm$ 0.07	0.22 $\pm$ 0.03
5	0.08 $\pm$ 0.01	0.13 $\pm$ 0.01
6	0.05 $\pm$ 0.00	0.10 $\pm$ 0.01
7	0.04 $\pm$ 0.01	0.09 $\pm$ 0.00
Total	54.47 $\pm$ 4.11	21.73 $\pm$ 0.73
DOGS (n = 3)		
Day	Urinary Excretion	Fecal Excretion
1	48.49 $\pm$ 11.32	3.06 $\pm$ 1.51
2	2.69 $\pm$ 0.56	3.57 $\pm$ 2.04
3	0.50 $\pm$ 0.05	0.37 $\pm$ 0.25
4	0.16 $\pm$ 0.00	0.30 $\pm$ 0.20
5	0.10 $\pm$ 0.03	0.08 $\pm$ 0.00
6	0.07 $\pm$ 0.02	0.13 $\pm$ 0.10
7	0.07 $\pm$ 0.02	0.13 $\pm$ 0.09
Total	52.06 $\pm$ 11.51	7.64 $\pm$ 1.10

TABLE A-2. TISSUE DISTRIBUTION IN ANIMALS OF  $^{14}\text{C}$ -LABELED AI3-35765  
7 DAYS AFTER A SINGLE INTRAVENOUS (I.V.) OR TOPICAL (P.C.) DOSE

Tissue	Rat, i.v.	Dog, i.v.	Rat, p.c.	Dog, p.c.
Liver	42.1	13.1	0.9	0.4
Kidney	5.2	6.8	2.0	*
Spleen	45.6	17.1	*	*
Heart	17.1	6.8	*	*
Lung	16.6	1.6	*	*
Brain	*	*	*	*
Adren Gland	10.3	4.4	1.6	*
Thyroid Gland	-	0.3	-	0.4
Urinary Bladder	0.4	*	*	*
Muscle	1.2	0.4	*	1.2
Bone	3.6	*	*	0.8
Skin	2.8	0.4	2.0	0.4
Fat	4.4	0.4	2.2	*
Testes	1.6	0.4	*	0.4
Bone Marrow	-	*	-	*
Bile	-	2.8	-	3.6
Blood	0.4	0.8	0.4	0.4

\*  $\leq$  Lower Limit of Detectability

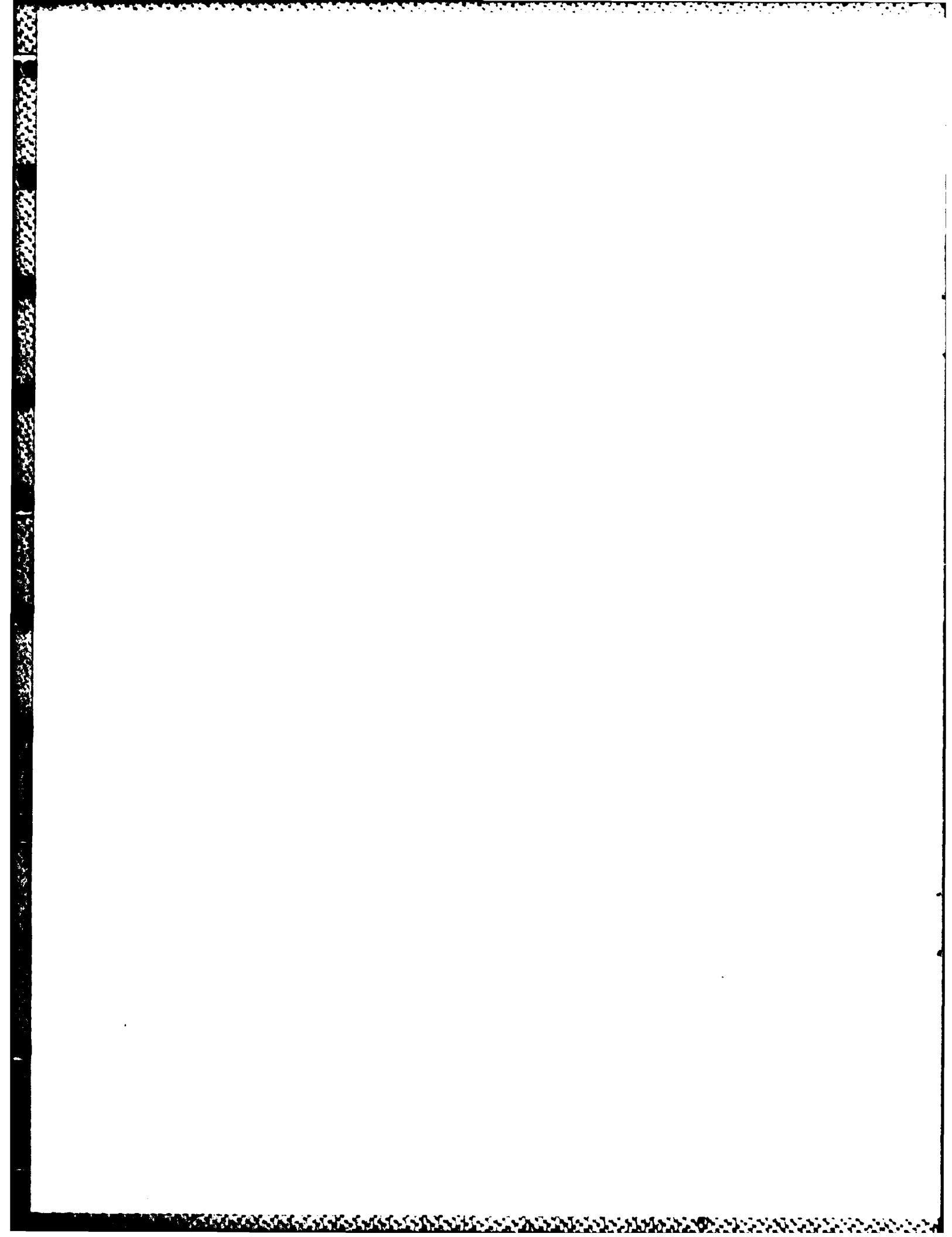
TABLE A-3. EXCRETION OF  $^{14}\text{C}$ -LABELED AI3-35765 FOLLOWING TOPICAL APPLICATION TO RATS AND DOGS

PERCENT OF APPLIED DOSE		
RATS (n = 5)		
Day	Urinary Excretion	Fecal Excretion
1	11.35 $\pm$ 5.04	2.30 $\pm$ 0.46
2	5.91 $\pm$ 0.96	2.90 $\pm$ 2.40
3	3.09 $\pm$ 1.71	1.25 $\pm$ 1.06
4	1.15 $\pm$ 0.41	1.06 $\pm$ 0.78
5	0.70 $\pm$ 0.44	0.76 $\pm$ 0.32
6	0.35 $\pm$ 0.21	0.41 $\pm$ 0.21
7	0.24 $\pm$ 0.13	0.26 $\pm$ 0.15
Total	22.80 $\pm$ 5.29	8.92 $\pm$ 2.90
DOGS (n = 3)		
Day	Urinary Excretion	Fecal Excretion
1	9.60 $\pm$ 1.83	0.26 $\pm$ 0.21
2	4.20 $\pm$ 1.11	0.42 $\pm$ 0.12
3	2.25 $\pm$ 0.62	0.40 $\pm$ 0.16
4	1.18 $\pm$ 0.18	0.37 $\pm$ 0.10
5	0.82 $\pm$ 0.39	0.20 $\pm$ 0.07
6	0.36 $\pm$ 0.24	0.15 $\pm$ 0.11
7	0.23 $\pm$ 0.07	0.22 $\pm$ 0.23
Total	18.63 $\pm$ 3.60	2.01 $\pm$ 0.40

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TABLE A-4. FATE OF  $^{14}\text{C}$ -LABELED AI3-35765 IN DOGS AND RATS 7 DAYS AFTER A SINGLE TOPICAL APPLICATION

% RECOVERY OF APPLIED DOSE		
	Rats, n = 5	Dogs, n = 3
Urine	22.80 $\pm$ 5.29	18.63 $\pm$ 3.60
Feces	8.92 $\pm$ 2.90	2.01 $\pm$ 0.40
<b>Total Absorbed</b>	<b>31.72 <math>\pm</math> 3.52</b>	<b>20.64 <math>\pm</math> 3.71</b>
Appl Site	0.77 $\pm$ 0.30	8.65 $\pm$ 4.16
24-Hr Patch	19.09 $\pm$ 4.26	18.92 $\pm$ 6.50
7-Day Patch	3.53 $\pm$ 1.72	22.96 $\pm$ 7.70
<b>Recovered Unabsorbed</b>	<b>23.39 <math>\pm</math> 5.97</b>	<b>50.53 <math>\pm</math> 6.13</b>
<b>Total Recovery</b>	<b>55.15 <math>\pm</math> 3.56</b>	<b>71.22 <math>\pm</math> 3.32</b>



APPENDIX B

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APPENDIX C

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following:

a. These studies were conducted in accordance with:

(1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.

(2) Title 21, Code of Federal Regulations (CFR), 1983 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

(3) Final Rule, Pesticide Programs; Good Laboratory Practice Standards; 48 Federal Register (FR) 53963-53969, 29 November 1983.

b. Facilities were inspected during its operational phase to ensure compliance with paragraph a above on 18, 19, 20, 21 October 1983, and draft report was reviewed 27-30 April 1984.

c. The information presented in this report accurately reflects the raw data generated during the course of conducting these studies.



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